Hierarchical Scaffolds for Bone Tissue Engineering and Repair Promote Rapid Bone Growth

The Pitch

Strategies for bone repair are currently based on the use of autografts or alloplastic (synthetic) materials. Both approaches have serious shortcomings. Bone grafting requires a second surgical site with the consequent risks to the patient and the amount of available bone is limited. Synthetic biomaterials often have integration problems with the host tissue and can result in infection, foreign-body reactions, and extrusion or loss of the implanted material. Their outcome is time-limited and unpredictable. In addition, one of the main functions of bone is mechanical support, and most synthetic implants for bone replacement or fracture repair in load-bearing situations are metals. These implants are stronger and stiffer than bone and shield the surrounding skeleton from its normal stress levels. This shielding of stresses by strong implants discourages the osteoblasts from continuously regenerating the bone. Bone resorption exceeds bone formation. The result is that the implant becomes loose over time as the surrounding tissue is resorbed.

An alternative that has attracted widespread attention in recent years is the engineering of new bone to replace the damaged or diseased tissue. A critical component of this tissue engineering approach is the development of porous three-dimensional structures—scaffolds—that will provide cell support and guide bone regeneration while substituting, at least temporarily, for the mineralized tissue. Although the field of tissue engineering emerged almost 15 years ago, progress has been slow. In the case of bone engineering, a major obstacle has been the inability to create scaffolds that fulfill the stringent physical and biological demands. In particular, one of the main problems is the combination of two apparently opposing requirements: a large open porosity needed to promote tissue ingrowth and the mechanical strength to substitute at least temporally for the natural tissue in load-bearing situations.

Researchers at Lawrence Berkeley National Laboratory (LBNL) are developing a new approach toward the fabrication of scaffolds based on the combination of novel processing technologies and different designs to create hierarchical structures that include lamellar materials and graded architectures. These developments are founded on the belief that a single scaffold design will not address all bone repair applications. From the standpoint of engineering, materials selection and scaffold design should be guided by the basic physical and biochemical requirements of the specific situation—particularly the anticipated mechanical loading during service.

The Technology

The two processing techniques employed are freeze-casting and robotic-assisted deposition. Freeze-casting involves the controlled directional freezing of ceramic and polymer-ceramic suspensions. Under these conditions, as the lamellar ice crystals grow they expel the ceramic particles and other molecules in the suspension. These accumulate in the areas between the ice crystals. A porous material forms with unique strength, which is derived from a lamellar architecture that mimics the structure of the inorganic component of nacre. The thickness of the lamellae can be controlled by manipulating the speed of the freezing front. This results in scaffolds with compressive strengths up to four times higher than that of materials with similar porosity fabricated using conventional techniques (see Figure 1a).

This creates the potential of using these scaffolds under load-bearing conditions. Robotic-assisted deposition is one of a new family of computer-aided fabrication techniques. In this technique, complex scaffolds can be built layer-by-layer following a computer design. This is accomplished by the controlled deposition of an ink with adequate properties to flow through a small nozzle under pressure then settling immediately afterwards to hold the weight and shape of the printed part (Figure 1b).

The researchers are using this technique to implement ceramic and polymer-ceramic scaffolds with graded designs inspired by the structure of bone. These are expected to provide mechanical support and an excellent environment for bone regeneration while also directing the formation of new tissue. Some examples of materials routinely prepared using these techniques are hydroxyapatite (HA), tricalcium phosphate (TCP), biphasic ceramics (HA-TCP), and hybrid polymer-ceramic composites based on polylactic and polycaprolactone polymers mixed with various calcium phosphates and bioactive glasses. Currently this work is being extended to incorporate engineered surfaces and drug delivery devices into the scaffolds.

Opportunities

The researchers and Lawrence Berkeley National Laboratory are seeking development partners and licensees for their technology for bone repair.

Source: For technical information: Eduardo Saiz, Lawrence Berkeley National Laboratory, Berkeley CA 94720, USA; 510-486-6202; and e-mail esaiz@lbl.gov; for licensing and partnership: Viviana Wolinsky, Lawrence Berkeley National Laboratory, Berkeley CA 94720, USA; 510-486-6463; and e-mail VIWolinsky@lbl.gov.
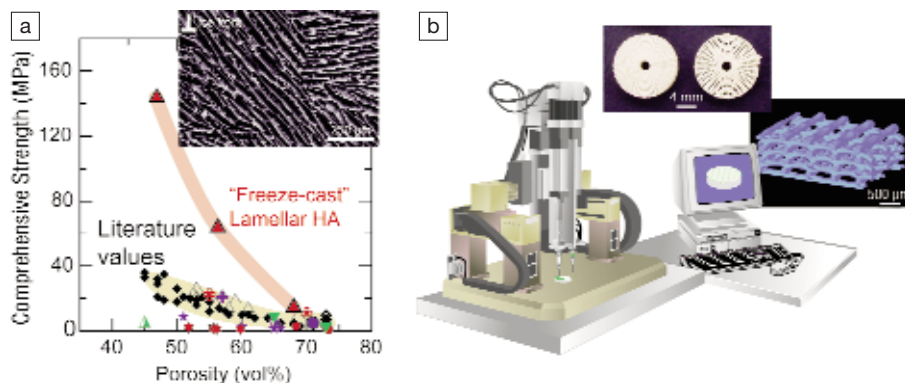

Figure 1. (a) Freeze-casting can be used to fabricate lamellar ceramic and polymer/ceramic scaffolds. Hydroxyapatite (HA) scaffolds prepared by freeze-casting exhibit strengths far superior to materials with similar porosity prepared using more conventional techniques. (b) Robotic-assisted deposition of ceramics and polymer/ceramic materials can be used to fabricate complex scaffolds that will incorporate structural gradients (e.g., radial gradients in porosity) to guide bone regeneration while providing mechanical support.

TECHNOLOGY ADVANCES seeks materials developments on the threshold of commercialization. Send suggestions to Renée G. Ford, Renford Communications, renford@comcast.net.

Graded Coatings Improve Adhesion to Dental and Orthopedic Implants

The Pitch

Annually, more than half a million people worldwide require orthopedic implants and in the United States, over one million people require bone graft procedures. Metals such as Ti or Co-Cr-based alloys have been used successfully for decades in fracture fixation, joint replacement, and dental applications. Various surface treatments have been developed to improve the ability of metallic alloys to bond to living tissues. These include surface roughening or applying diverse coatings. Animal studies have shown that, compared to uncoated implants, implants with a thin layer of calcium phosphate (CP) have markedly enhanced interfacial attachment to bone over short periods of time. Also, numerous histological studies provide evidence that coated implants yield a more reliable interface with bone than mechanical osseointegration. Benefits arise during healing and the subsequent bone remodeling including faster healing time, enhanced bone formation, firmer implant-bone attachment, and a reduction of metallic ion release.

Although bioactive coatings can improve implant performance, research is still far from the development of optimum materials and fabrication technologies. Current coating technologies such as plasma spray or calcium phosphates have serious shortcomings that have limited their application. Most of those are related to their weak adhesion to the substrate and poor long-term stability as well as to difficulties in achieving an accurate compositional control.

Bioactive glasses are a very attractive alternative for the coating of implants since they exhibit excellent adhesion to bone. However, initial attempts to coat metallic implants with the original bioactive glass, Bioglass®, have failed to produce stable layers due to the generation of large thermal expansion stresses and high reactivity between the metal and the glass. The solution to the problem requires the development of adequate coating procedures and novel bioactive glasses and glass-ceramics with the appropriate thermal expansion coefficients and softening points. Researchers at Lawrence Berkeley National Laboratory (LBNL) have developed a new family of bioactive glasses in the system Si-Ca-Mg-Na-K-P-O with thermal expansion coefficients similar to those of the alloys used in orthopedic implants and relatively low softening points (all below 900°C).

The Technology

The LBNL glasses can be used to coat metallic implants using a simple enameling technique. Strong glass/metal adhesion is achieved through the formation of thin interfacial layers (shown in Figure 1a). Glass-based coatings offer unique versatility as their composition—and therefore their properties—can be easily manipulated. However, using bioactive glass coatings has a critical drawback. By their own nature, bioactive glasses are susceptible to slow crack growth that can be detrimental to their long-term stability. To overcome this problem, the researchers have developed a procedure to fabricate graded coatings through the sequential deposition of different glass and glass-ceramic layers combined with enameling.

The graded approach allows the design of coatings that will combine a highly stable metal-glass interface with a bioactive surface layer. For example, using this process, graded coatings on Ti and Co-Cr alloys can be fabricated consisting of a high-silica glass in contact with the metal and a composite surface layer that consists of a mixture of a low-silica glass with synthetic micrometer-sized hydroxyapatite (HA) particles. The high-silica layer is very resistant to corrosion in body fluids; it provides good coating adhesion and long-term stability, while the surface layer is designed to enhance coating attachment to the tissue. Typical coating thicknesses range between 10 μm to 200 μm.

After immersion in simulated body fluid, the coatings can generate hydroxyapatite (a calcium phosphate closely related to the mineral component of the bone) *in vitro* through a complex dissolution-precipitation process. Analysis in cell cultures has shown that they are highly biocompatible and can promote mineralization and affect indirectly osteoblast gene expression through their dissolution products. This opens the possibility of designing glasses with controlled ion release *in vivo* to further influence osteogenesis.

Preliminary *in vivo* tests have been performed using Ti-based implants. The histopathology evaluation revealed a significant trend with time in bone quality improvement in the coated implants. In addition, the coatings apparently accelerate the integration of the device to the surrounding bone tissues facilitating the transformation of woven bone matrix to lamellar type over a two- to six-month time period. Mechanical analysis revealed that the coatings maintained excellent adhesion to the metal after the *in vivo* testing and no detached particulates were found in the bone-implant interface vicinity (Figure 1b). Currently, the researchers are working to extend this technology to coat diverse technical ceramics and tissue engineering scaffolds.
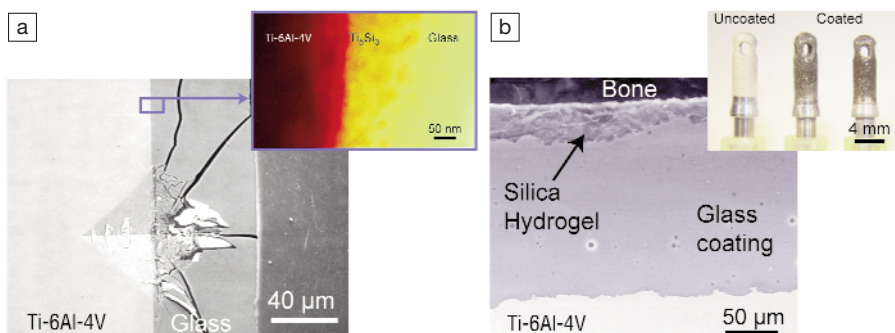

Figure 1. (a) The enameling process results in the formation of thin interfacial layers that provide excellent adhesion to the metal (as shown in the indentation test where the cracks travel through the coating but not through the interface). (b) Adhesion is maintained after *in vivo* tests of coated implants.

Opportunities

The researchers and Lawrence Berkeley National Laboratory are seeking development partners and licensees for their coating technology.

Source: For technical information: Eduardo Saiz, Lawrence Berkeley National Laboratory, Berkeley CA 94720, USA; 510-486-6202; and e-mail esaiz@lbl.gov; for licensing and partnership: Viviana Wolinsky, Lawrence Berkeley National Laboratory, Berkeley CA 94720, USA; 510-486-6463; and e-mail VIWolinsky@lbl.gov.

Ultrathin Polymer Coatings Accomplished by Vapor Deposition

The Pitch

GVD Corporation is commercializing a novel technology for manufacturing ultrathin polymer coatings. This technology addresses the need for solventless, scalable, low-cost polymer coatings in applications ranging from biomedical implants to portable electronics to aerospace structures. Traditional wet-deposition methods for polymers are complicated by the need for solvents and high-temperature curing, and typically result in thicker coatings. Thick, wet-applied coatings can obscure fine geometries such as those found on microelectromechanical systems (MEMS) devices, membranes, and other complex parts. In contrast, GVD's dry, vapor deposition process produces extremely thin, adherent polymer coatings on an almost unlimited variety of surfaces. The process neither requires the coated parts to be heated, nor does it require polymer curing. As a result, temperature-sensitive plastics and even paper can be coated with ease.

Although many polymers can be deposited by conventional spray-, dip-, or spin-coating from solution or the molten state, certain specialty polymers do not dissolve (e.g., non-stick polytetrafluoroethylene, PTFE) and/or do not melt. This makes it difficult to produce smooth, uniform coatings by wet application methods without compromising the polymers' performance. Conventional vapor deposition is a solventless, gas-phase technique that does produce thin, uniform coatings and is well suited for parts with small surface features. For example, inorganic coatings (e.g., polysilicon, silicon oxide/nitride) are often deposited in the semiconductor industry using this method. However, the harsh process conditions used in conventional vapor deposition (e.g., plasma activation, high substrate temperatures) typically preclude the production of high-quality polymer coatings. Notably, GVD's technology combines the performance benefits of wet-applied polymer coatings with the process benefits of clean, all-dry vapor deposition.

The Technology

GVD's technology is called "initiated chemical vapor deposition (iCVD), and it was invented by Karen Gleason at the Massachusetts Institute of Technology. iCVD can produce a wide variety of well-known polymers. For example, GVD is commercializing non-stick PTFE fluoropolymer, electrically conducting PEDOT (poly-3,4-ethylenedioxythiophene), and biocompatible silicone coatings, among others. In iCVD, a vapor-phase initiator is thermally activated and combined with monomer vapor to induce polymerization on the surface of the coated part. iCVD coating thickness is precisely controlled and is typically in the range of 10 nm to 10 μm. Because the process occurs at low pressure and uses gaseous reagents, the resulting GVD coatings conform to parts with complex topologies like molds. The reactive vapors also penetrate fabrics, foams, and membranes, forming thin polymer coatings on contact and gently "shrink-wrapping" the part's surface features. Even nanosized particles such as carbon nanotubes can be individually coated using iCVD, as shown in Figure 1.

The parts remain cool (≤40°C during most iCVD processes) and, since no solvents are used, no drying is required. iCVD thus eliminates the high costs associated with solvent purchase, storage, handling, and disposal, and reduces processing time. Solvent-sensitive substrates (e.g., polystyrene) and fine features (e.g., MEMs components, which might otherwise be damaged by capillary forces during solvent drying) can be coated. Polymer deposition rates are high and the process uses low reagent flow rates and low power (<500 W). This makes iCVD both efficient and environmentally friendly.

Opportunities

In addition to its iCVD coatings, GVD has also developed large-scale equipment for coating to lease to customers operating under a license. GVD is actively looking for partners who need pure, ultrathin, conformal polymer coatings and would like to evaluate the iCVD technology.

Source: Hilton G. Pryce Lewis or Erik S. Handy, GVD Corporation, 45 Spinelli Place, Cambridge, MA 02138, USA; 617-661-0060 ext. 11; e-mail info@gvdcorp.com; and Web site www.gvdcorp.com.
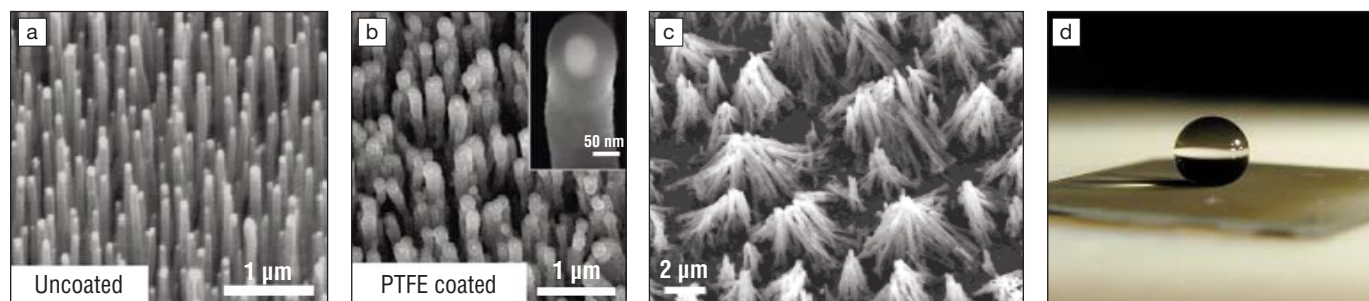

Figure 1. Carbon nanotubes (50 nm diameter, 2 μm height) (a) uncoated, and (b) coated with 40 nm of GVD's PTFE coating. The PTFE coating "shrink-wraps" high-aspect-ratio features without the use of solvent. Uncoated tubes (c) agglomerate after exposure to water and evaporative drying due to capillary effects, while coated tubes (d) show superhydrophobicity due to the combination of low surface energy and roughness. Reprinted with permission from K.K.S. Lau et al., *Nano Lett.* **3** (12) 2003, p. 1701. © 2003 American Chemical Society. (Collaboration with K. Teo, W. Milne, J. Robertson, University of Cambridge, UK)